

**PLASTER FOR PERCUTANEOUSLY ABSORBING ESTRADIOL**

**Patent number:** JP5148145  
**Publication date:** 1993-06-15  
**Inventor:** HIRANO MUNEHIKO; NIIMURA MIYUKI; TATEISHI TETSUO; NAKAGAWA AKIRA  
**Applicant:** HISAMITSU PHARMACEUTICAL CO  
**Classification:**  
- **international:** A61K9/70; A61K31/565  
- **European:**  
**Application number:** JP19910341921 19911130  
**Priority number(s):** JP19910341921 19911130

**Report a data error here**

**Abstract of JP5148145**

**PURPOSE:** To provide a plaster percutaneously absorbing estradiol continuously releasing the estradiol and not causing flares, rashes, etc., by adding the estradiol as an active ingredient to a base agent component containing an elastic polymer. **CONSTITUTION:** The objective plaster contains an (A-B)<sub>n</sub>-A type elastic polymer (A is monovinyl-substituted aromatic compound polymer block; B is conjugated diolefin copolymer block; (n) is 3-7), polyethylene glycol, a fatty acid ester and a water-absorbing polymer as essential components, and also estradiol as an active ingredient. The plaster contains preferably 5-50wt.% of the elastic polymer (e.g. styrene-isoprene-styrene block copolymer), 1-10wt.% of the polyethylene glycol (e.g. polyethylene glycol 200), 1-10wt.% of the fatty acid ester (e.g. ethyl oleate), 1-20wt.% of the water-absorbing polymer (e.g. traded name: Sumikagel SP-520) and 0.01-10wt.% of the estradiol.

---

Data supplied from the **esp@cenet** database - Worldwide

## PATENT ABSTRACTS OF JAPAN

(11)Publication number : 05-148145  
 (43)Date of publication of application : 15.06.1993

---

(51)Int.CI. A61K 31/565  
 A61K 9/70  
 A61K 9/70

---

(21)Application number : 03-341921 (71)Applicant : HISAMITSU PHARMACEUT CO INC  
 (22)Date of filing : 30.11.1991 (72)Inventor : HIRANO MUNEHIKO  
 NIIMURA MIYUKI  
 TATEISHI TETSUO  
 NAKAGAWA AKIRA

---

## (54) PLASTER FOR PERCUTANEOUSLY ABSORBING ESTRADIOL

## (57)Abstract:

PURPOSE: To provide a plaster percutaneously absorbing estradiol continuously releasing the estradiol and not causing flares, rashes, etc., by adding the estradiol as an active ingredient to a base agent component containing an elastic polymer.

CONSTITUTION: The objective plaster contains an (A-B)<sub>n</sub>-A type elastic polymer (A is monovinyl-substituted aromatic compound polymer block; B is conjugated diolefin copolymer block; (n) is 3-7), polyethylene glycol, a fatty acid ester and a water-absorbing polymer as essential components, and also estradiol as an active ingredient. The plaster contains preferably 5-50wt.% of the elastic polymer (e.g. styrene-isoprene-styrene block copolymer), 1-10wt.% of the polyethylene glycol (e.g. polyethylene glycol 200), 1-10wt.% of the fatty acid ester (e.g. ethyl oleate), 1-20wt.% of the water-absorbing polymer (e.g. traded name: Sumikagel SP-520) and 0.01-10wt.% of the estradiol.

## LEGAL STATUS

[Date of request for examination] 26.02.1996

[Date of sending the examiner's decision of rejection]

[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]

[Date of final disposal for application]

[Patent number] 2971224

[Date of registration] 27.08.1999

[Number of appeal against examiner's decision of rejection]

[Date of requesting appeal against examiner's decision of rejection]

[Date of extinction of right]

Copyright (C); 1998,2003 Japan Patent Office

**\* NOTICES \***

JPO and NCIPI are not responsible for any  
damages caused by the use of this translation.

1. This document has been translated by computer. So the translation may not reflect the original precisely.
- 2.\*\*\*\* shows the word which can not be translated.
3. In the drawings, any words are not translated.

---

**CLAIMS**

---

**[Claim(s)]**

[Claim 1] They are the estradiol percutaneous absorption patches which a basis component uses a polyethylene glycol [ polymer / n-A (A-B) mold elastic / [among a formula, a mono-vinyl permutation aromatic compound polymer block and B express a conjugation diolefin copolymer block, and, as for n, A expresses the integer of 3-7 substantially] ], fatty acid ester, and a water absorption giant molecule as an indispensable component, and come to contain estradiol as a drug effect component in estradiol percutaneous absorption pharmaceutical preparation.

[Claim 2] Estradiol percutaneous absorption patches according to claim 1 characterized by containing 0.01 – 10 % of the weight of estradiols which are 5 – 50 % of the weight of n-A mold elastic polymers, 1 – 10 % of the weight of polyethylene glycols, 1 – 10 % of the weight of fatty acid ester, 1 – 20 % of the weight of water absorption giant molecules, and a drug effect component as a basis component (A-B).

---

[Translation done.]

\* NOTICES \*

JPO and NCIPI are not responsible for any damages caused by the use of this translation.

1. This document has been translated by computer. So the translation may not reflect the original precisely.
2. \*\*\*\* shows the word which can not be translated.
3. In the drawings, any words are not translated.

---

DETAILED DESCRIPTION

---

[Detailed Description of the Invention]

[0001]

[Industrial Application] This invention relates to suitable estradiol percutaneous absorption patches to emit estradiol continuously.

[0002]

[Description of the Prior Art] Estradiol is estrogen (estrogen) secreted from the ovary at the stage when it can reproduce female. Therefore, the woman before and behind a menopause mainly causes lack of estradiol, and which symptom with unusual menopausal disorders and menstruation produces her. Although the cure by an oral agent etc. is performed for the object which improves these symptoms now, since alimentary canals, liver, etc., such as the stomach and intestines, are metabolized promptly and it is inactivated, in order to expect sufficient drug effect manifestation, high-dose estradiol must be taken. Moreover, there is a possibility that manifestation nature, such as a side effect, may increase for a high dose.

[0003] Then, the medication method for the dermal administration which does not go via an alimentary canal, liver, etc. is examined. For example, patches are not indicated [ that the percutaneous absorption pharmaceutical preparation which contains menthol as penetration enhancer is only indicated, and ] at all by the approach of controlling bleedoff for the estradiol which is dissolving in the gel of hydroxypropylcellulose-ethanol by the ethylene-vinyl acetate film, and JP,60-152413,A at JP,57-154122,A.

[0004] The remedy constituent using the drug transparency accelerator which comes to mix propylene glycol and a glycerol to a certain specific ratio is stated to JP,61-17513,A. The patches which use as a principal component the polymer which can be swollen as an adhesion basis in underwater [, such as adhesive resin ingredients (polyterpene resin, hydrocarbon resin, etc.), natural rubber or synthetic rubber (a polyisobutylene and styrene-butylene polymer, a styrene-isoprene polymer, a styrene-ethylene-butylene

polymer, 1, 4-polyisoprene, etc.), and galactomannan, ] are indicated by JP,61-155321,A. The patches about the device which consists of a seven-layer layered product are indicated by JP,63-233916,A.

[0005]

[Problem(s) to be Solved by the Invention] The estradiol percutaneous absorption patches to which various examination is performed as mentioned above need a special process for the manufacture one for complicated structure, and a manufacturing facility becomes high. Only the limited rate is used but the active substance contained in respect of others has low extent of bioavailability. Furthermore, addition of absorption enhancers, such as ethanol, etc. has a problem in respect of a skin stimulus from the field of medicating transderma. the above trouble -- taking an example -- this invention persons -- 1 -- as a result of continuing examination wholeheartedly for the purpose of offering the estradiol percutaneous absorption patches aiming at reduction of an improvement 3 skin stimulus of structure 2 simple extent of bioavailability, it results in completion of this invention.

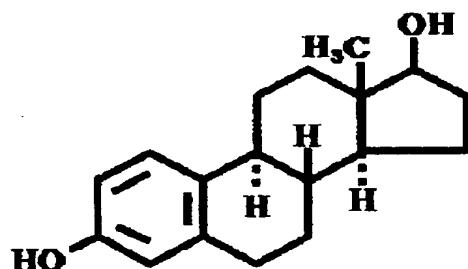
[0006]

[Means for Solving the Problem] namely, the estradiol percutaneous absorption patches of this invention -- as the base (A-B) of 1 pharmaceutical preparation -- a n·A mold elastic polymer [among a formula, a mono-vinyl permutation aromatic compound polymer block and B express a conjugation diolefin copolymer block, and, as for n, A expresses the integer of 3·7 substantially]

2) Contain polyethylene-glycol 3 fatty-acid-ester 4 water absorbing polymer as an indispensable component. The estradiol used for this invention is generic name S truck-1.3.5 (10) trien-3.17beta-diol, and it is shown by the following structure expression.

[0007]

[Formula 1]



Estra-1,3,5(10)-trien-3,17β-diol

The content of this estradiol is 0.01 - 10 % of the weight in estradiol percutaneous absorption patches. It is 0.05 - 5 % of the weight preferably. It is 0.1 - 1 % of the weight still more preferably.

[0008] In this invention, the n·A mold elastic polymer used as the pharmaceutical preparation base (A·B) The styrene·butadiene·styrene block copolymer made from shell chemistry which can specifically come to hand easily as a commercial item (caliph REXX TR·1101), A styrene·isoprene·styrene block copolymer (caliph REXX TR·1107, caliph REXX TR·1111) etc., Although the styrene·isoprene·styrene block copolymer (JSR5000) by Japan Synthetic Rubber Co., Ltd. and the Queen tuck 3421 grade by Nippon Zeon Co., Ltd. are mentioned, a styrene·isoprene·styrene block copolymer is used especially suitably. By using such (A·B) a n·A mold elastic polymer as the pharmaceutical preparation base, bleedoff of estradiol and large improvement in extent of bioavailability can be aimed at.

[0009] As for the polyethylene glycol used in this invention, a polyethylene glycol 200, a polyethylene glycol 300, a polyethylene glycol 400, a polyethylene glycol 600, a polyethylene glycol 1000, a polyethylene glycol 1500, a polyethylene glycol 1540, and a polyethylene glycol 4000 are specifically used suitably.

[0010] As for the fatty acid ester used in this invention, ethyl oleate, myristic·acid isopropyl, palmitic·acid isopropyl, butyl stearate, myristic·acid Millis Chill, myristic·acid octyldodecyl, stearin acid cholesteryl, and adipic·acid diisopropyl are specifically used suitably.

[0011] Combination of the polyethylene glycol and fatty acid ester which are used for this invention raises substantially the solubility of estradiol, the bleedoff from pharmaceutical preparation, percutaneous absorption, etc. Moreover, there is no example by which a polyethylene glycol and fatty acid ester were blended with n·A mold elastic polymer base pharmaceutical preparation as the resolvent of estradiol and absorption enhancers (A·B), and the well-known reference which suggests it is not found, either.

[0012] The water absorption macromolecule used for this invention absorbs the water of 10 times or more of a self·weight, and carries out gelation swelling, it is the thing of pulverized coal preferably, for example, a thing or a starch acrylonitrile graft saponification object metal salt etc. which introduced the slight crosslinking bond into polyacrylic acid and its metal salt, for example, sodium salt, the carboxymethyl·ized polyvinyl alcohol, a carboxymethyl cellulose and its metal salt, a carboxymethyl polymer, etc. is used, and such pulverized coal is used preferably.

[0013] concrete -- Mitsuhiro -- formation -- AKUA Made from make SANUETTO

[IM-300, IM-1000, IM-1000MPS, etc. Steel] Chemistry -- ARASOBU made from SUMIKAGERU [SP-520, SP-540, N-100, NP-1020, and NP-1040 grade] Arakawa Chemistry by 4S, 4SH, etc. Sumitomo Chemical Co., Ltd. [ keeping / [Co., Ltd.] ] [800,800F grade] is used.

[0014] The rubor by stimulus of MURE by improvement in a utilization factor, sweating at the time of pasting, etc. and a drug etc. and sharp reduction of \*\*\*\*\* can be aimed at by using the base material component which uses these elastic bodies, a polyethylene glycol, fatty acid ester, and a water absorption macromolecule as an indispensable component.

[0015] The desirable content of a n·A (A·B) mold elastic polymer, a polyethylene glycol, fatty acid ester, and a water absorption macromolecule is as follows among the estradiol percutaneous absorption patches of this invention.

[0016] That is, the total amount of the content of the indispensable component which consists of a n·A (A·B) mold elastic polymer, a polyethylene glycol, fatty acid ester, and a water absorbing polymer is 30 · 60 % of the weight still more preferably 20 to 99% of the weight among pharmaceutical preparation. further -- the content of each component -- under pharmaceutical preparation (A·B) -- it is [ 3 · 10 % of the weight, and 1 · 15 % of the weight of fatty acid ester ] 2 · 10 % of the weight still more preferably still more preferably 3 · 10 % of the weight, and 1 · 20 % of the weight of water absorption macromolecules still still more preferably more preferably [ 5 · 50 % of the weight of n·A mold elastic polymers / 10 · 20 % of the weight, and 1 · 15 % of the weight of polyethylene glycols ], and the combination of this range expresses the effectiveness of this invention most.

[0017] In addition to the above-mentioned indispensable component, \*\*\*\* optimum dose content of the combination of softeners, such as a well-known liquid paraffin, a tackifier, and an inorganic bulking agent is carried out conventionally at the estradiol percutaneous absorption pharmaceutical preparation of this invention. Moreover, what does not have effect in bleedoff of a drug and is excellent in flexibility as a base material of the pharmaceutical preparation of this invention is desirable, and compound raw materials, such as a plastic film with the flexibility by which it is chosen out of films, such as polyester, polypropylene, and poly CHIREN, or textile fabrics, and aluminum foil, or these were stretched, or textile fabrics, are desirable.

[0018] Next, the manufacturing method of the estradiol percutaneous absorption pharmaceutical preparation of this invention is explained. First, after carrying out the heating dissolution of the basis component, a drug, a polyethylene glycol, and fatty acid ester are added, and it \*\*\*\* to the above-mentioned base material, and it can also once

make with the \*\*\*\* back on the film with which it made with the cutting product in the bonnet and the desired configuration at the liner, or exfoliation processing was performed, and can also make with an imprint sticking-by-pressure product to a suitable base material. Thus, the estradiol percutaneous absorption patches of obtained this invention have the effectiveness of \*\*\*\*\* for the skin stimulus in repetitive administration and chronic administration substantially while they raise bleedoff of the estradiol which is a content drug and raise extent of bioavailability.

[0019]

[Example] Hereafter, an example and the example of a trial are given and this invention is explained more to a detail. In addition, that all it is with the "section" mean the weight section among an example, the example of a comparison, and the example of reference.

[0020] Example 1 Styrene-isoprene-styrene block copolymer The 35.00 sections (trade name caliph REXX TR-1107)

A liquid paraffin The 57.99 sections Polyethylene glycol 200 The 1.00 sections Ethyl oleate The 1.00 sections Water absorbing polymer (SUMIKAGERU SP-520) The 5.00 section Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.01 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0021] Example 2 Styrene-isoprene-styrene block copolymer The 35.00 sections (trade name caliph REXX TR-1107)

A liquid paraffin The 51.50 sections Polyethylene glycol 300 The 5.00 sections Ethyl oleate The 3.00 sections Water absorbing polymer (SUMIKAGERU SP-520) The 5.00 section Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0022] Example 3 Styrene-isoprene-styrene block copolymer The 30.00 sections (trade name caliph REXX TR-1107)

A liquid paraffin The 35.00 sections Polyethylene glycol 400 The 10.00 sections Myristic-acid isopropyl The 10.00 sections Water absorbing polymer (SUMIKAGERU SP-520) The 5.00 sections Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 10.00 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0023] Example 4 Styrene-isoprene-styrene block copolymer The 35.00 sections (trade name caliph REXX TR-1107)

A liquid paraffin The 53.50 sections Polyethylene glycol 600 The 6.00 sections

Palmitic acid isopropyl The 4.00 sections Water absorbing polymer (trade name AKUA keeping 4SH) The 1.00 section Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0024] Example 5 Styrene-isoprene-styrene block copolymer The 20.00 sections (trade name caliph REXX TR-1107)

A liquid paraffin The 47.50 sections Polyethylene glycol 1000 The 5.00 sections Butyl stearate The 7.00 sections Water absorbing polymer (trade name AKUA keeping 4SH) The 20.00 section Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0025] Example 6 Styrene-isoprene-styrene block copolymer The 35.00 sections (trade name caliph REXX TR-1107)

A liquid paraffin The 45.50 sections Polyethylene glycol 1500 The 7.00 sections Myristic acid Millis Chill The 7.00 sections Water absorbing polymer (trade name ARASOBU 800F) The 5.00 section Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0026] Example 7 Styrene-isoprene-styrene block copolymer The 35.00 sections (trade name caliph REXX TR-1107)

A liquid paraffin The 49.50 sections Polyethylene glycol 200 The 4.00 sections Myristic acid octyldodecyl The 6.00 sections Water absorbing polymer (trade name ARASOBU S-100F) The 5.00 section Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0027] Example 8 Styrene-isoprene-styrene block copolymer The 35.00 sections (trade name caliph REXX TR-1107)

A liquid paraffin The 51.50 sections Polyethylene glycol 300 The 5.00 sections Stearin acid cholestryl The 3.00 sections Water absorbing polymer (trade name SANUETTO IM-300MPS) The 5.00 sections Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0028] Example 9 Styrene-isoprene-styrene block copolymer The 35.00 sections (trade name caliph REXX TR-1107)

A liquid paraffin The 45.50 sections Polyethylene glycol 400 The 7.00 sections Adipic acid diisopropyl The 7.00 sections Water absorbing polymer (trade name

SANUETTO IM-1000MPS) The 5.00 sections Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0029] Example 10 Styrene-isoprene-styrene block copolymer The 25.00 sections (trade name caliph REXX TR-1107)

Liquid paraffin The 34.50 sections Polyethylene glycol 600 The 5.00 sections Ethyl oleate The 5.00 sections Water absorbing polymer (trade name SANUETTO IM-1000MPS) The 5.00 sections Tackifier (alicyclic group saturated hydrocarbon resin) The 25.00 sections (trade name Al Cong P-100)

Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0030] Example 11 Styrene-isoprene-styrene block copolymer The 5.00 sections (trade name caliph REXX TR-1107)

A liquid paraffin The 42.50 sections Polyethylene glycol 1000 The 4.00 sections Myristic-acid isopropyl The 8.00 sections Water absorbing polymer (trade name SANUETTO IM-1000MPS) The 5.00 sections Tackifier (alicyclic group saturated hydrocarbon resin) The 35.00 sections (trade name Al Cong P-100)

Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0031] Example 12 Styrene-isoprene-styrene block copolymer The 50.00 sections (trade name caliph REXX TR-1107)

A liquid paraffin The 22.00 sections Polyethylene glycol 1500 The 7.00 sections Palmitic-acid isopropyl The 3.00 sections Water absorbing polymer (trade name SANUETTO IM-1000MPS) The 5.00 sections Tackifier (alicyclic group saturated hydrocarbon resin) The 12.50 sections (trade name Al Cong P-100)

Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0032] Example 13 Styrene-isoprene-styrene block copolymer The 27.00 sections (trade name caliph REXX TR-1107)

A liquid paraffin The 38.50 sections Polyethylene glycol 300 The 2.00 sections Butyl stearate The 2.00 sections Water absorbing polymer (trade name SANUETTO IM-1000MPS) The 5.00 sections Tackifier (rosin ester) The 25.00 sections (trade name KE-311)

Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0033] Example 14 Styrene-isoprene-styrene block copolymer The 26.50 sections (trade name caliph REXX TR-1107)

A liquid paraffin The 36.00 sections Polyethylene glycol 300 The 5.00 sections Myristic-acid Millis Chill The 5.00 sections Water absorbing polymer (trade name SANUETTO IM-1000MPS) The 2.00 sections Tackifier (rosin ester) The 25.00 sections (trade name KE-311)

Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0034] Example 15 Styrene-isoprene-styrene block copolymer The 25.00 sections (trade name caliph REXX TR-1107)

A liquid paraffin The 32.50 sections Polyethylene glycol 400 The 5.00 sections Myristic-acid octyldodecyl The 7.00 sections Water absorbing polymer (trade name SANUETTO IM-1000MPS) The 5.00 sections Tackifier (rosin ester) The 25.00 sections (trade name KE-311)

Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0035] Example 16 Styrene-isoprene-styrene block copolymer The 22.50 sections (trade name ) [ caliph REXX TR-1107 liquid paraffin ] The 30.00 sections Polyethylene glycol 400 The 7.00 sections Stearin acid cholestryl The 5.00 sections The water absorbing polymer (trade name SANUETTO IM-1000MPS) 10.00 section Tackifier (rosin ester) The 25.00 sections (trade name KE-311)

Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0036] Example 17 Styrene-isoprene-styrene block copolymer The 22.50 sections (trade name caliph REXX TR-1107)

A liquid paraffin The 27.00 sections Polyethylene glycol 600 The 10.00 sections Adipic-acid diisopropyl The 10.00 sections Water absorbing polymer (trade name SANUETTO IM-1000MPS) The 5.00 sections Tackifier (rosin ester) The 25.00 sections (trade name KE-311)

Estradiol According to the above-mentioned manufacturing method, it produced by the

formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0037] Example 18 Styrene-isoprene-styrene block copolymer The 25.00 sections (trade name caliph REXX TR-1107)

A liquid paraffin The 33.50 sections Polyethylene glycol 600 The 8.00 sections Ethyl oleate The 3.00 sections Water absorbing polymer (trade name SANUETTO IM-1000MPS) The 5.00 sections Tackifier (alicyclic group saturated hydrocarbon resin) The 25.00 sections (trade name Al Cong P-100)

Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0038] Example 19 Styrene-isoprene-styrene block copolymer The 25.00 sections (trade name caliph REXX TR-1111)

A liquid paraffin The 34.50 sections Polyethylene glycol 1000 The 2.00 sections Myristic-acid isopropyl The 8.00 sections Water absorbing polymer (trade name SANUETTO IM-1000MPS) The 5.00 sections Tackifier (alicyclic group saturated hydrocarbon resin) The 25.00 sections (trade name Al Cong P-100)

Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0039] Example 20 Styrene-isoprene-styrene block copolymer The 22.50 sections (trade name caliph REXX TR-1107)

A polyisobutylene The 5.00 sections Liquid paraffin The 29.00 sections Polyethylene glycol 1000 The 10.00 sections Palmitic-acid isopropyl The 3.00 sections Water absorbing polymer (trade name SANUETTO IM-1000MPS) The 5.00 sections Tackifier (alicyclic group saturated hydrocarbon resin) The 25.00 sections (trade name Al Cong P-100)

Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0040] Example 21 Styrene-isoprene-styrene block copolymer The 22.50 sections (trade name caliph REXX TR-1111)

A polyisobutylene The 5.00 sections Liquid paraffin The 32.00 sections Polyethylene glycol 1500 The 6.00 sections Butyl stearate The 4.00 sections The water absorbing polymer (trade name SANUETTO IM-1000MPS) 5.00 section Tackifier (alicyclic group saturated hydrocarbon resin) The 25.00 sections (trade name Al Cong P-100)

Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0041] Example 22 Styrene-isoprene-styrene block copolymer The 25.00 sections (trade name caliph REXX TR-1111)

Liquid paraffin The 29.50 sections Polyethylene glycol 1500 The 7.00 sections Myristic-acid Millis Chill The 8.00 sections Water absorbing polymer (trade name SANUETTO IM-1000MPS) The 5.00 sections Tackifier (rosin ester) The 25.00 sections (trade name KE-311)

Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0042] Example 23 Styrene-isoprene-styrene block copolymer The 22.50 sections (trade name caliph REXX TR-1107)

A polyisobutylene The 5.00 sections Liquid paraffin The 32.00 sections Polyethylene glycol 300 The 3.00 sections Ethyl oleate The 7.00 sections Water absorbing polymer (trade name SANUETTO IM-1000MPS) The 5.00 sections Tackifier (rosin ester) The 25.00 sections (trade name KE-311)

Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0043] Example 24 Styrene-isoprene-styrene block copolymer The 22.50 sections (trade name caliph REXX TR-1111)

A polyisobutylene The 5.00 sections Liquid paraffin The 32.00 sections Polyethylene glycol 400 The 5.00 sections Myristic-acid isopropyl The 5.00 sections Water absorbing polymer (trade name SANUETTO IM-1000MPS) The 5.00 sections Tackifier (rosin ester) The 25.00 sections (trade name KE-311)

Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0044] Example 1 of a comparison Styrene-isoprene-styrene block copolymer The 25.00 sections (trade name caliph REXX TR-1107)

A polyisobutylene The 5.00 sections Liquid paraffin The 32.50 sections Polyethylene glycol 300 The 5.00 sections Myristic-acid Millis Chill The 7.00 sections Tackifier (rosin ester) The 25.00 sections (trade name KE-311)

Estradiol According to the above-mentioned manufacturing method, it produced by the

formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0045] Example 2 of a comparison Styrene-isoprene-styrene block copolymer The 25.00 sections (trade name caliph REXX TR-1107)

Polyisobutylene The 5.00 sections Liquid paraffin The 39.50 sections Water absorbing polymer (trade name SANUETTO IM-1000MPS) The 5.00 sections Tackifier (rosin ester) The 25.00 sections (trade name KE-311)

Estradiol According to the above-mentioned manufacturing method, it produced by the formula of 0.50 \*\*\*\*, cut in desired magnitude, and considered as estradiol percutaneous absorption patches.

[0046] Example 1 of reference Acrylic resin system solvent mold pressure sensitive adhesive The 93.16 sections (trade name NISSETSU PE-300 40% of solid content) (after [ desiccation ] 84.47 section)

Polyethylene glycol 300 The 2.21 sections (after [ desiccation ] 5.01 section)

Ethyl oleate The 2.21 sections (after [ desiccation ] 5.01 section)

Water absorbing polymer (trade name SUMIKAGERU SP-520) The 2.21 sections (after [ desiccation ] 5.01 section)

Estradiol The 0.22 sections (after [ desiccation ] 0.50 section)

After mixing by this formula, it \*\*\*\*(ed) at the above-mentioned base material or the liner so that the plaster body thickness after solvent evaporation might become being the same as that of an example, and according to the above-mentioned manufacturing method, it produced henceforth, it was cut in desired magnitude, and was made into estradiol percutaneous absorption patches.

[0047] Example 2 of reference Silicone binder The 80.50 sections (trade name milt contest 355Medical Adhesive)

A polyethylene glycol 300 The 5.00 sections Ethyl oleate The 7.00 sections Water absorbing polymer (trade name SUMIKAGERU SP-520) The 7.00 sections Estradiol After mixing by the formula of 0.50 \*\*\*\*, it \*\*\*\*(ed) at the above-mentioned base material or the liner so that plaster body thickness might become being the same as that of an example, and according to the above-mentioned manufacturing method, it produced henceforth, it was cut in desired magnitude, and was made into estradiol percutaneous absorption patches.

[0048] The example 1 (hair loess mouse skin radiographic examination 1) of a trial using an example 2 and the examples 1 and 2 of reference, a hair loess mouse skin radiographic examination is performed, and a test result is looked like [ drawing 1 ] and shown. As shown in a test result, the example 2 shows that bleedoff of estradiol is

clearly high as compared with the examples 1 and 2 of reference. This originates in the pharmaceutical preparation of this invention using a n-A mold elastic polymer, a polyethylene glycol, and fatty acid ester as a basis component (A·B). That is, the usefulness of this invention is supported.

[0049] The example 2 (hair loess mouse skin radiographic examination 2) of a trial Using examples 15, 17, and 23 and the example 2 of a comparison, a hair loess mouse skin radiographic examination is performed, and a result is shown in drawing 2. As shown in a test result, examples 15, 17, and 23 show that bleedoff of estradiol is clearly high as compared with the example 2 of a comparison. The pharmaceutical preparation of this invention originates in this using a polyethylene glycol and fatty acid ester. That is, the usefulness of this invention is supported.

[0050] The example 3 (skin stimulation test) of a trial example 14- using 16, 23, and the example 1 of a comparison, for 3.5 days, it stuck and the condition of the skin was observed to a 15 healthy adult men child's thorax. it is shown in a table 1 -- as -- example 14- the effectiveness there are few skin stimuli clearly and according [ 16 and 23 ] to combination of a water absorption macromolecule as compared with the example 1 of a comparison, has shown up. That is, the usefulness of this invention is supported.

[0051]

[A table 1]

	-	±	+	++	合 計	陽性率 ±以上%
実施例14	12	2	0	0	15	13.3
実施例15	14	1	0	0	15	6.7
実施例16	14	1	0	0	15	6.7
実施例23	14	1	0	0	15	6.7
比較例 1	4	3	4	4	15	73.3

In addition, the skin stimulus criterion is as follows.

with no change ; · feeble rubor ; \*\* -- clear rubor ; the inside of + critical -- blurring ; ++

[0052] The example 4 (rabbit blood·drug·concentration measurement trial) of a trial

Rabbit blood-drug-concentration measurement was performed using examples 15, 17, and 23 and the example 2 of a comparison. The hair of a Japanese white house rabbit in back was removed, and the estradiol concentration in blood was measured with time. A test result is shown in drawing 3. As shown in a test result, as compared with the example 2 of a comparison, it is turning around examples 15, 17, and 23 on the rear spring supporter to the standups of blood drug concentration, burst sizes, and all the durability. That is, the usefulness of this invention is supported.

[0053]

[Effect of the Invention] the pharmaceutical preparation in which the estradiol percutaneous absorption patches of this invention which contains a n·A (A·B) mold elastic polymer, and a polyethylene glycol, fatty acid ester and a water absorption giant molecule as an indispensable component were most suitable for bleedoff of estradiol as explained above -- becoming -- sufficient drug effect -- discovered -- moreover -- the rubor -- it can fog -- etc. -- it is dramatically useful on industry as just ideal estradiol percutaneous absorption patches which are not.

---

[Translation done.]